Selective hematopoietic stem cell ablation using CD117-antibody-drug-conjugates enables safe and effective transplantation with immunity preservation.

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Public Summary:
Blood stem cell transplantation is a curative therapy for many blood and immune diseases with potential for many settings beyond current standard-of-care. Use of blood stem cell transplantation across a wider patient group is currently precluded largely due to morbidity and mortality associated with toxic radiation or chemotherapy used to allow the donor blood stem cells to engraft. Here we show that a single dose of an antibody that targets a molecule call CD117 which has been attached to a drug called saporin (compound referred to as CD117-anti-drug conjugate or CD117-ADC) leads to > 99% depletion of recipients stem cells, enabling rapid and efficient donor blood cell engraftment. Importantly, the CD117-ADC agent selectively targets blood stem cells yet does not cause clinically significant side-effects. Blood counts and immune cell function were preserved following CD117-ADC treatment, with effective responses by recipients to infectious pathogens, specifically viral and fungal challenges. These results suggest that CD117-ADC-mediated stem cell transplant pre-treatment could serve as a non-safer and gentler strategy for the treatment of a wide range of non-malignant and malignant diseases, and might be especially suited to gene therapy and gene editing settings in which preservation of immunity is desired.

Scientific Abstract:
Hematopoietic stem cell transplantation (HSCT) is a curative therapy for blood and immune diseases with potential for many settings beyond current standard-of-care. Broad HSCT application is currently precluded largely due to morbidity and mortality associated with genotoxic irradiation or chemotherapy conditioning. Here we show that a single dose of a CD117-antibody-drug-conjugate (CD117-ADC) to saporin leads to > 99% depletion of host HSCs, enabling rapid and efficient donor hematopoietic cell engraftment. Importantly, CD117-ADC selectively targets hematopoietic stem cells yet does not cause clinically significant side-effects. Blood counts and immune cell function are preserved following CD117-ADC treatment, with effective responses by recipients to both viral and fungal challenges. These results suggest that CD117-ADC-mediated HSCT pre-treatment could serve as a non-myeloablative conditioning strategy for the treatment of a wide range of non-malignant and malignant diseases, and might be especially suited to gene therapy and gene editing settings in which preservation of immunity is desired.

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